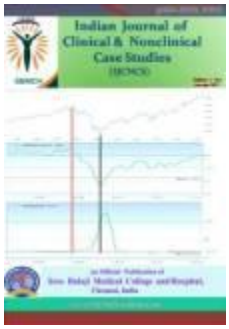

Indian Journal of Clinical and Non clinical Case Studies
Article.No.5(2), 2019:
IJCNCS : ISSN.2456-8163

POLYCYTHEMIA VERA –A RARE PRESENTATION

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ABSTRACT:

Polycythemia vera is a clonal disorder consisting of multipotent hematopoietic progenitor cells and in the absence of physiological stimulus, red cells, granulocytes and platelets accumulate and thus form a Polycythemia vera. It occurs predominantly in woman in 2.5 per 100000 persons and may increase with age. only 1% of patients with polycythemia vera exhibited bleeding gums and such symptoms are attributed to hyper-viscosity of blood. In the present case, polycythemia vera patient was admitted with symptoms of gum bleeding as an unusual presentation

KEY WORDS: polycythemia vera, JAK 2 mutation, hyperviscosity, erythropoietin

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CASE STUDY:

A 58 year old female had come to op section of SBMCH with c/o generalized weakness, headache, dizziness, occasional bleeding of gums for more than 1 month. There was no history of blurring of vision, tinnitus, vomiting, and breathlessness.

On examination, patient was found to be alert, oriented, and afebrile

Vitals: BP – 170/100 mmHg – Rt. upper limb, 170/100 mmHg – Lt. upper limb

PR : 72/min, regular. All peripheral pulses felt equally.

No pallor, icterus, clubbing, cyanosis, lymphadenopathy, oedema.

CVS – S1S2+,RS – NVBS, Clear, abdomen – Soft, Non-tender, noorganomegaly.

CNS – No focal deficit.

Laboratory investigations revealed the occurrence of Hb – 17.7 gm/dl, RBC count – 7.31 millions/cu mm, Platelet count – 6.69 lakhs/cu mm,Total count – 18080 cells/cumm, PCV – 63.7 %.

Red cell indices:

MCV – 87.1 fl, MCH – 24.2 pg, MCHC – 27.8%, Total bilirubin 0.5 mg/dl, Direct bilirubin 0.1 mg/dl, Indirect bilirubin 0.4 mg/dl,SGOT – 31 IU/L,SGPT – 12 IU/L,ALP – 146 IU/L,Total protein – 7.4 gm/dl, Albumin – 4.2 gm/dl, GGT – 20 IU/L, Renal function test showed normal kidney.

Serum T3: 1.20 ng/ml (Ref. range: 0.8 – 2), Serum T4: 8.43ug/dl (Ref. range: 5.1 – 14.1),Serum TSH: 3.610 uIU/ml. Serum Cancer Antigen 125: 12.2 U/mL (Ref. range: Less than 35)

RBC : Normocytic, Normochromic cells were seen.

WBC: Increased in number of WBC; neutrophils exhibited toxic changes, eosinophils also increased in number.

Platelets: Increased in number of platelets. No hemoparasite seen.

Impression: Neutrophilic leucocytosis with eosinophilia and reactive thrombocytosis were noted. PT INR: 1.33 (Normal: 0.9 – 1.1), Ferritin: 12.5 ng/ml (Ref. range: Male: 30 – 400; Female: 13 – 150)

Bone marrow aspiration revealed a dry tap.

Erythropoietin (EPO) : 1.93 mIU/mL (Ref. range: 3.7 – 31.5 mIU/mL)

JAK2 (Janus kinase-2 gene) mutation: V617F mutation in exon 14 of JAK2 gene was detected in the leukocytes

Our investigations revealed a marked increase in hemoglobin, PCV and hematocrit, and these data indicated the occurrence of polycythemia in the current case. Further evaluation supported the occurrence of primary polycythemia which was eventually confirmed by JAK2 exon 14 mutation assays. Thus our studies confirmed that the patient was suffering from Polycythemia vera.

In this case, JAK2 Exon 14 mutation Assay was used to detect (the occurrence of mutation of JAK2V617 while a high level expression of erythropoietin (Epo) was taken as an indicator of erythrocytosis in the case. The mutation in JAK2V617F and presence of low levels of Epo indicated it to be a case of PV ((JAK2 V617F mutation is positive in 97% of PV patients).

Soon after the diagnosis, the patient was treated for venesection after which the patients have recovered well from the symptoms.

DISCUSSION:

Polycythemia vera is a clonal disorder involving a multipotent hematopoietic progenitor cells. In the absence of physiological stimulus red cells, granulocytes and platelets were accumulating. Polycythemia vera occurs in 2.5 per 100000 persons increasing with age. Women predominately show sporadic cases of Polycythemia vera though the etiology remains unknown. No consistent cytogenetic abnormality has been shown to be associated with polycythemia vera. JAK2 mutation could play a central role in pathogenesis of polycythemia vera. If the

JAK2V617F mutation is positive and Epo level is low, then the diagnosis of PV may be confirmed (JAK2 V617F mutation is positive in 97% of PV patients). JAK2 is an indispensable kinase in the erythropoitin (EPO) receptor signal transduction pathway. Constitutive JAK2 kinase activity shall result in EPO-independent proliferation of the erythrocyte precursors. JAK2[1] is also involved in the JAK2-STAT5 pathways of the thrombopoietin receptor (MPL) and the Granulocyte colony-stimulating factor receptor (GCSF-R). A V617F mutation can lead to proliferation of multiple cell lines, therefore patients with PV often have elevated platelets and leukocyte as well. JAK2[2] may be directly involved in the intracellular signaling following exposure to cytokines to which polycythemia vera progenitor cells display hypersensitivity.

ETIOLOGY:

PRIMARY POLCYTHEMIA:

Polycythemia rubravera

Decrease in EPO

SECONDARY POLYCYTHEMIA:

Caused by physiologically appropriate increase in erythropoitein

Inappropriate increase in erythropoietin

APPROPRIATE EPO INCREASE:

High altitudes

Pulmonary disease and alveolar hypoventilation

Congenital cardiovascular diseases

Familial congenital polycythemia

Heavy cigarette smoking

INAPPROPRIATE EPO INCREASE:

Renal carcinoma

Uterine tumors, HCC

DIAGNOSTIC CRITERIA OF PV:

MAJOR WHO CRITERIA:

Hemoglobin > 18.5 g/dL in men and > 16.5 g/dL in women, or other evidence of increased red blood cell volume

Presence of JAK2 V617F or other functionally similar mutation, such as JAK2 exon 14 mutation

Elevated RBC accumulation > 25% mean normal predicted value

Hb or Hct > 99th percentile of method-specific reference range for age, sex

MINOR CRITERIA

Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) and prominent erythroid, granulocytic, and megakaryocytic proliferation

Serum erythropoietin level shall be less than the reference range for normal

Endogenous erythroid colony formation shall occur *in vitro*

The only history positive for this patient was presence of bleeding gums and headache. Patient was also a newly diagnosed hypertensive.

Investigations showed elevated Hb, PCV, RBC and platelets

Decreased EPO, and JAK2 mutation was detected.

Arterial oxygen saturation – Normal

After ruling out all the secondary causes of polycythemia, a most appropriate diagnosis of primary polycythemia was made.

Patient was treated by doing phlebotomy, ~400 – 500ml per week.

After subsequent episodes of phlebotomy, she became symptomatically better.

Currently the patient is in regular follow up.

The word polycythemia indicates increase in RBCs, WBCs and platelets. Mostly it indicates an increase in pure RBCs alone or erythrocythemia which is a more specific term.

Relative polycythemia can also result from decreased plasma volume.

True polycythemia is due to an increase in the RBC mass. It is included in a group of diseases which are known asmyeloproliferative disorders (MPD)

Polycythemia is a Chronic myeloproliferative disorder (CMPD) which is characterised by proliferation of one or more myeloid cell lineages.Can also be called as panmyelosis as it involves increased production of all 3 cell lines. Most common of the myeloproliferativedisorders.Incidence is more common in men.

According to the WHO Classification of Hematopoietic and Lymphoid Neoplasms [3] 2008 myeloproliferative neoplasms are divided into categories by diagnostic characteristics

Chronic myelogenous leukemia (CML)

Essential thrombocythemia (ET)

Polycythemia vera (PV)

Primary myelofibrosis (PMF)

SYMPTOMS

Usually insidious in onset with symptoms of headache, dizziness,vertigo,tinnitus,visual disturbances, angina pectoris, intermittent claudication.

SIGNS

Splenomegaly,hepatomegaly,plethora or ruddy complexion,pruritus,erythromelalgia-palms & feet may become red, warm tender and hypertension .

COMPLICATIONS

Bleeding complications:

epistaxis, gum bleeding, ecchymoses, and gastrointestinal (GI) bleeding.

Thrombotic complications

venous thrombosis or thromboembolism, increased prevalence of stroke , other arterial thrombosis.

Budd-chiari syndrome

Over time, polycythemia vera may convert to myelofibrosis or to CML. In approximately 5% of cases, PV progresses to AML, which is usually refractory to therapy.

MANAGEMENT[4]

Aspirin

Phlebotomy

Myelosuppressive therapy:

Hydroxyurea: acts to decrease all three blood lines. Long term use can lead to leukemogenesis (~15 years). May cause nausea, vomiting, constipation, and diarrhoea are very common with doses >60mg/kg

Interferon-alpha: decreases both the red cell number and the frequency of thrombo-haemorrhagic events. It affects the stem cell compartment, and reversal of JAK2 mutational status can be seen. It must be administered subcutaneously and can cause fever, arthralgias, myalgias, alopecia, anorexia, peripheral neuropathies, and depression. ACE inhibitors should be avoided with interferon-alpha, as this may lead to granulocytopenia and thrombocytopenia.

Recent advances:

JAK2 Inhibitors -Ruxolitinib (Jakafi)

Anagrelide – primarily effects platelet production and is more commonly used in PV for thrombocytosis. S/e includes palpitations, tachycardia, nausea, diarrhoea and fluid retention.

Prognosis:

Patients with polycythemia vera who are treated, have a mortality rate similar to age-matched controls.

Death is secondary to thrombosis in 30-40% patients.

Myelofibrosis is the cause of death in ~5% of patients, and haemorrhage is the cause in 2-10% of patients.

CONCLUSION:

Polycythemia vera is a clonal disorder involving a multipotent hematopoietic [5] progenitor cells. In the absence of physiological stimulus, red cells, granulocytes and platelets are known to accumulate. Polycythemiavera occurs in 2.5 per 100000 persons with increasing age. Women predominate in sporadic cases. Only 1% of patients with polycythemia vera exhibited bleeding gums which is attributed to hyper-viscosity of blood. We presented a case of polycythemia vera admitted with symptoms of gum bleeding which is an unusual presentation

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